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Is it time for a paradigm shift in drug research and development in endometriosis/adenomyosis?

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Abstract

BACKGROUND:The drug research and development (R&D) for endometriosis/adenomyosis has been painfully slow. Most completed clinical trials on endometriosis did not publish their results, and presumably failed. While few published trials did report how they foundered, the reasons why they failed are often completely unclear. Surprisingly, there has been no open discussion on why these trials failed. If the causes for these failed trials remain unelucidated, mistakes made in these failed trials may be repeated in the future. Since failure can be infinitely more instructive and educational than success, elucidating the causes for failed clinical trials may yield a treasure trove for future drug R&D. Given our growing understanding of the natural history of ectopic endometrium, it is also important to make an inventory of biologicals/compounds that are currently under development to see where we stand and whether they would stand a better chance of gaining regulatory approval than their predecessors.

OBJECTIVE AND RATIONALE:We provide an overview of all compounds under clinical investigation and in development in order to assess the evolution of R&D since the last inventory, reported in 2013. We also have attempted to analyse selected failed clinical trials in the context of published translational/preclinical research and our growing understanding of the natural history of

endometriotic/adenomyotic lesions, in the hope that the lessons learned will steer investigators toward the right track in future drug R&D.

SEARCH METHODS:We searched ClinicalTrials.gov and a database containing information on drugs gathered daily by Thomson Reuters from a wide range of sources (e.g. patent offices, biomedical literature, congresses, symposia, meetings, company information, regulatory information) for all therapeutic compounds that have undergone or are under clinical trials, or in the developmental stage, and then searched PubMed and Google to determine their publication status using trial identifiers. For trials that were completed at least 2 years ago and have, or have not, published their results, a PubMed search was performed using the name of the therapeutic that has been tested and 'endometriosis' or 'adenomyosis' to identify published preclinical studies prior to the launch of the trial. For those published trials, the cited preclinical studies were also retrieved and scrutinized.

OUTCOMES: Despite repeated calls for more transparency, only a small fraction of completed trials on endometriosis has been published. A large number of 'novel' compounds under development are simply repurposed drugs, which seem to be ill-prepared to combat the fibroproliferative nature of endometriosis/adenomyosis. This sobering picture indicates an alarming innovation 'drought' in the drug R&D front, resulting in trickling drug pipelines. Some trials foundered owing to unanticipated serious side-effects, or because attempts were made to suppress a target that can be compensated for by redundant pathways, but many failed in efficacy, indicating that the translational value of the current models is seriously questionable. All existing animal models of endometriosis do not recapitulate the key features of human conditions.

WIDER IMPLICATIONS:The glaring innovation drought in drug R&D for endometriosis/adenomyosis should sound alarms to all stake-holders. The failed clinical trials in endometriosis also indicate that some past research had serious deficiencies. In light of the recent understanding of the natural history of ectopic endometrium, it is perhaps time to shift the research paradigm and revamp our research focus and priorities.